NCCN 10th Annual Congress:
Hematologic Malignancies™

PET-Guided Treatment Approach for Advanced Stage Classical Hodgkin Lymphoma

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Management of Hodgkin Lymphoma
Learning Objectives

- Review risk adapted strategies based on PET/CT response for optimizing front line management
- Evaluate data on incorporation of new agents in front line therapy

Hodgkin Lymphoma Clinical Trial Treatment Groups

Europe vs North America

Europe (GSHG, GELA, EORTC)	Stage	USA/Canada
Early favorable	CS I,IIA,B No risk factors	Limited stage
Early unfavorable	CS I,IIA,B	
(Intermediate)	B Sx ESR>50 mm Bulky disease >2-3 nodal sites Men over 40 y of age	
Advanced stage	CS III – IV, Selected CS IIB	Advanced stage

Courtesy Dr Connors

Management of Hodgkin Lymphoma

Expected treatment outcomes and goals of Rx - 2015

Stage	Cure Rate	Goals of Rx
Early Stage		
Favorable (stage I-II)	90%	↓ toxicity
Unfavorable (stage I, II with risk factors*)	80-85%	↑ efficacy
Advanced stage (bulky IIB, III, IV)	75%	↑ efficacy

* Large mediastinal mass, E lesions, ≥ 3 nodal sites, ↑ ESR; age >40, MC histology

PET/CT Imaging
Potential Uses for Hodgkin Lymphoma

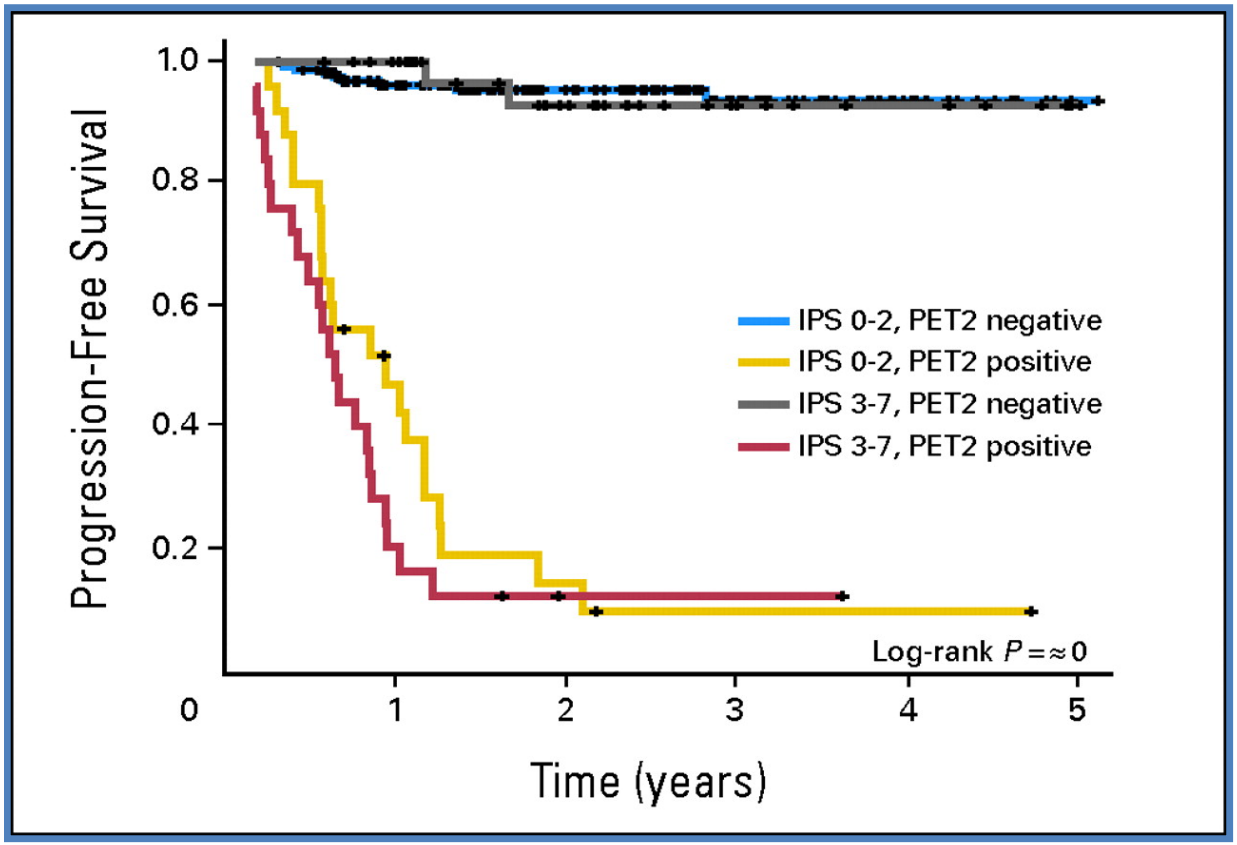
- Staging: YES
- Response assessment: YES
  - End of therapy (EOT)

- Treatment modification based on PET/CT
  - EOT
  - Interim

- Can modification of Rx based on EOT or interim PET/CT have the potential to select pts for Rx escalation or de-escalation?
- Do these modifications have the potential to improve outcomes?

Advanced Hodgkin Lymphoma

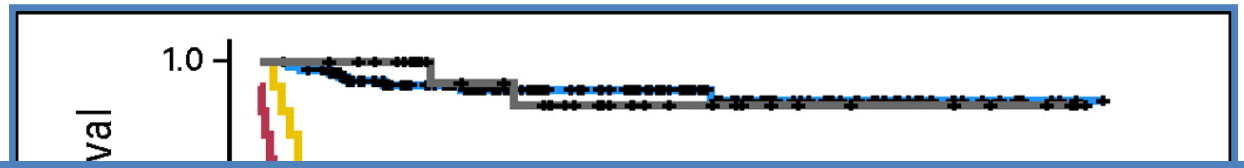
Interim PET Imaging after ABVD x 2



Gallamini et al JCO 2007

Advanced Hodgkin Lymphoma

Interim PET Imaging after ABVD x 2



Deauville 5-point scoring system

Score Uptake

1 No uptake

2 Uptake ≤ mediastinum

3 Uptake > mediastinum but ≤ liver

4 Uptake moderately higher than liver

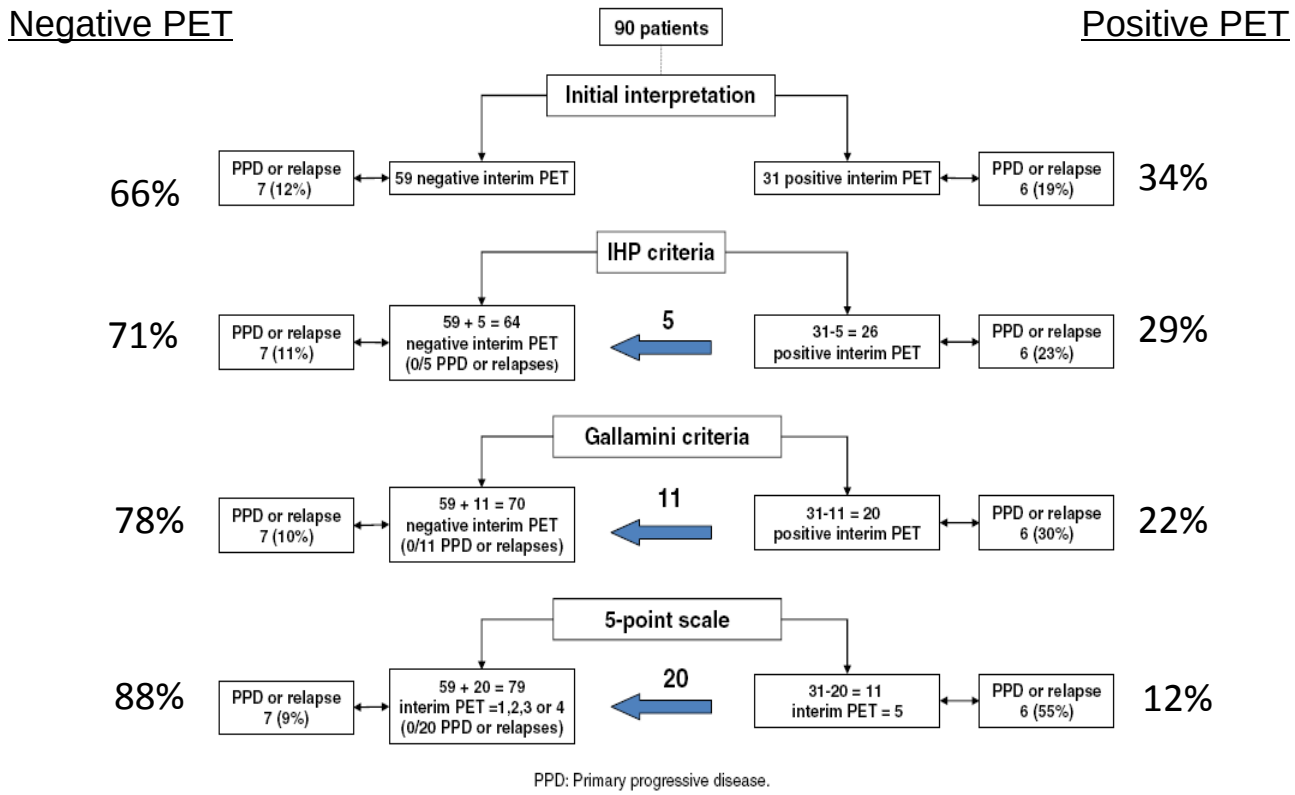
5 Uptake markedly higher than liver and/or new lesions

X New areas of uptake unlikely to be related to lymphoma

J Clin Oncol 2014; 32 (27): 3048-3058

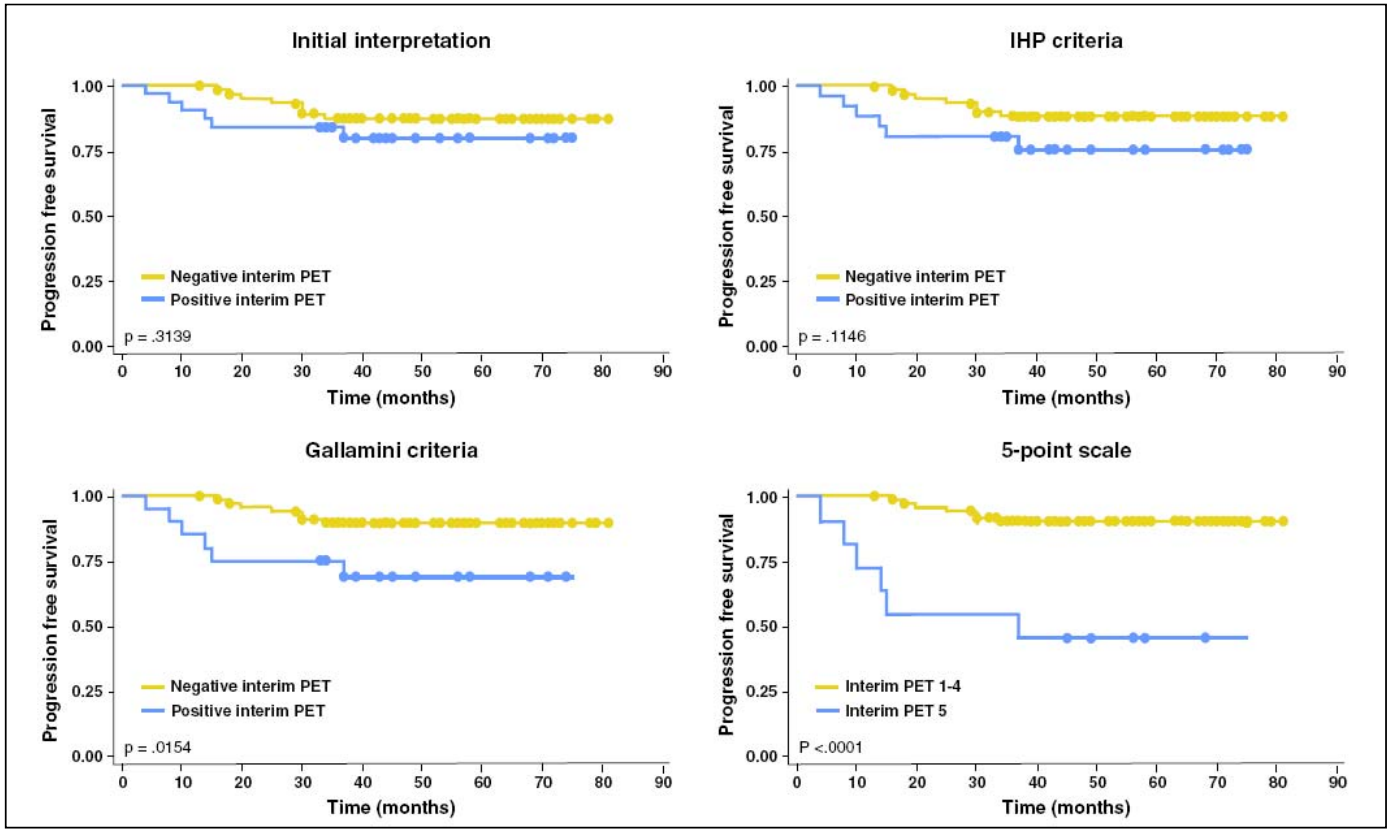
Gallamini et al JCO 2007

Predictive value of interim PET/CT varies according to the criteria used



Le Roux Eur J Nucl Med Mol Imaging 2011

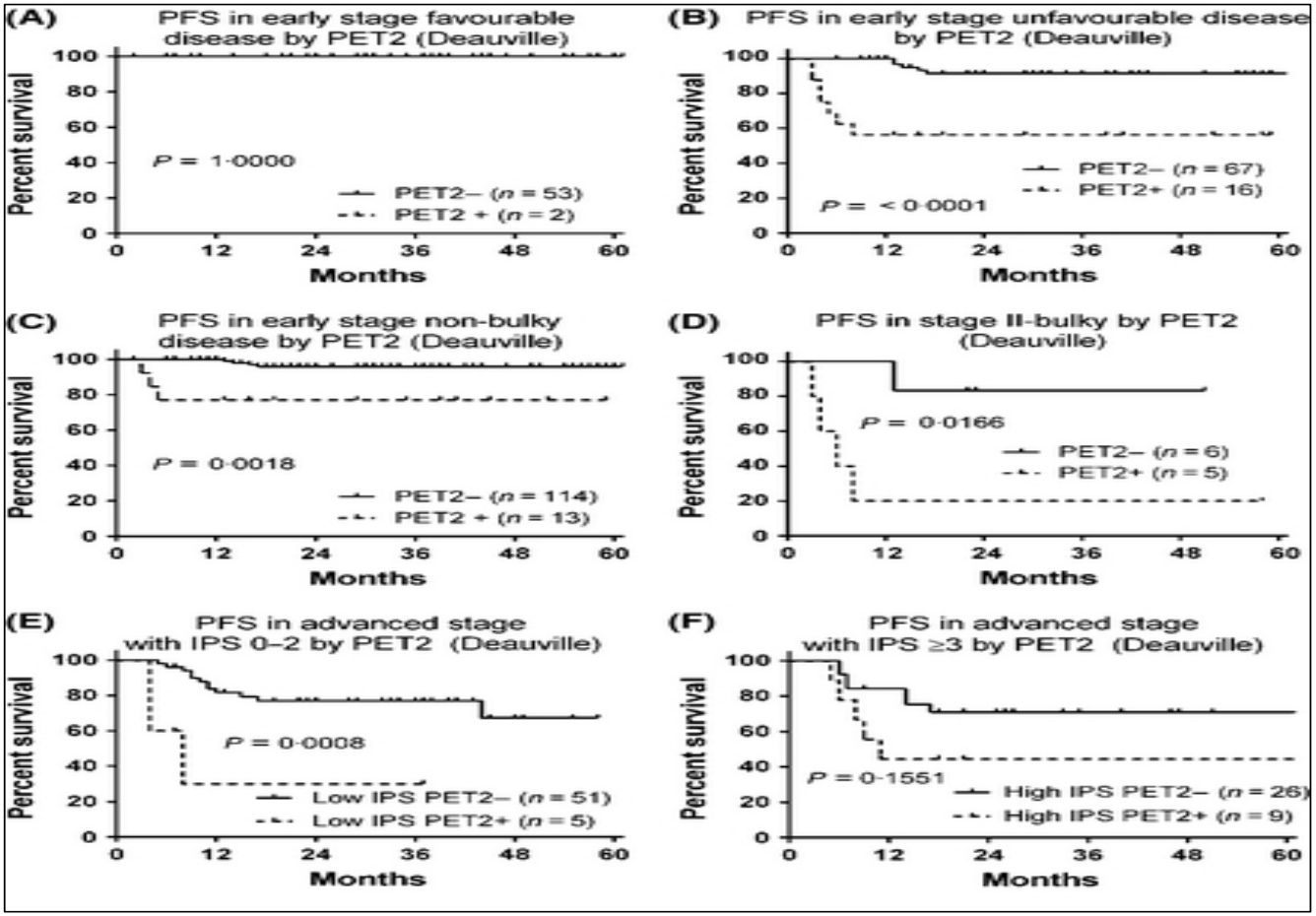
Variation in PFS Among the Same Patients Based on Differences in PET Definitions



Le Roux Eur J Nucl Med Mol Imaging 2011

The prognostic value of interim PET scan in patients with classical Hodgkin lymphoma

MD Anderson Retrospective study using Deauville Criteria

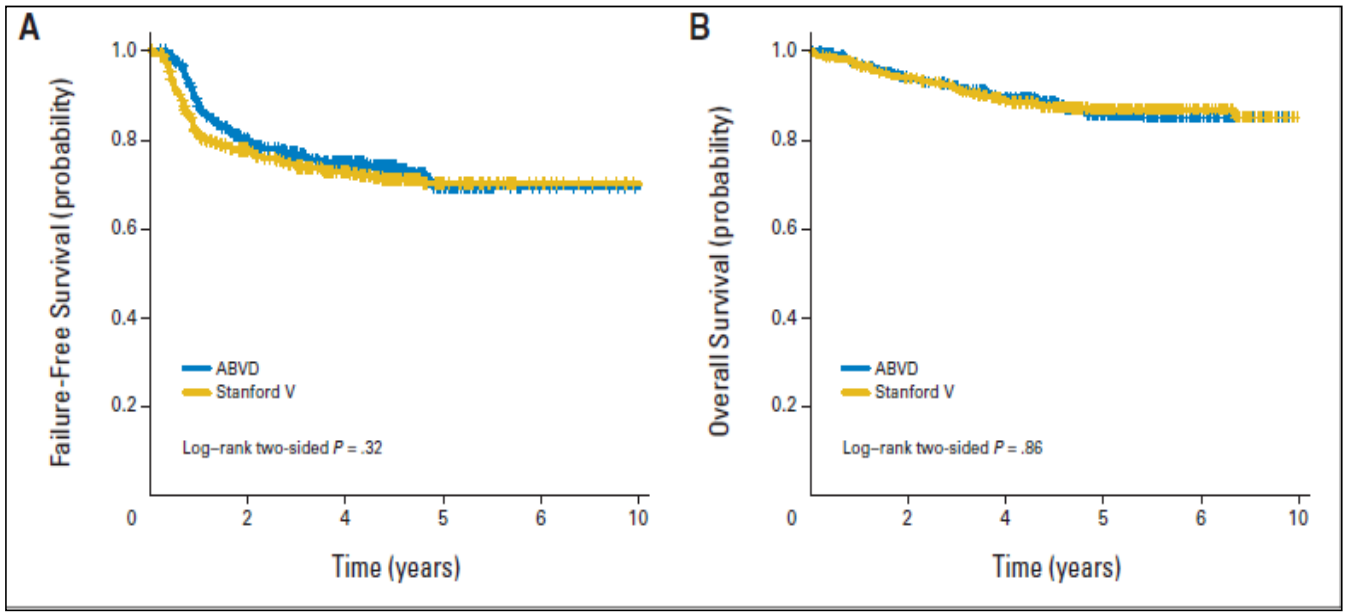


Oki et al Br J Hematol 2014;165:112-116

Advanced Hodgkin Lymphoma

ABVD chemotherapy

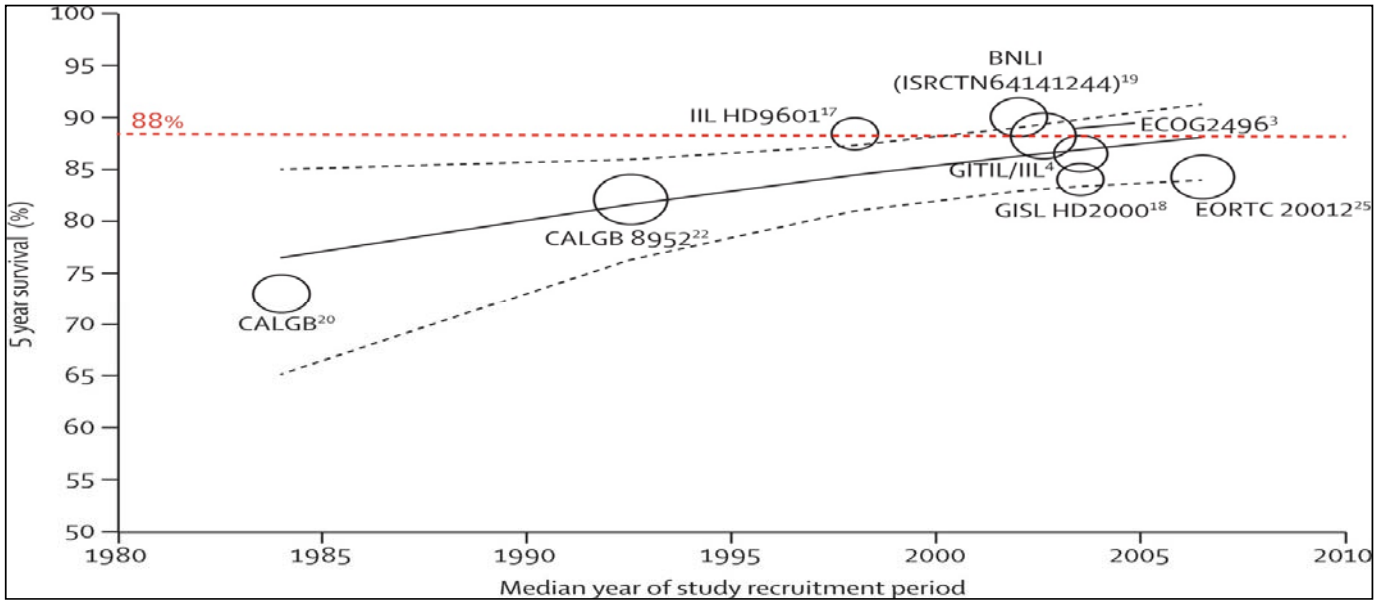
A standard therapy based on balance of efficacy and toxicity



Gordon et al J. Clin Oncol 2013; 31:684-691

Effect of Initial Rx Strategy on OS of pts with Advanced-Stage HL: A Systematic Review and Network Meta-analysis

5 year OS with ABVD, according to year of recruitment



- Position of each circle: proportion of pts achieving 5 year OS
- Size of the circle: weight in the meta-regression
- Dashed horizontal straight line: proportion of pts given ABVD with OS 5 y (used as ref)
- Solid line: pooled 5 year survival for ABVD

Skoetz et al The Lancet Oncology, 2013, 943 - 952

Advanced Hodgkin Lymphoma

- Esc BEACOPP(BE): Intense German Regimen
  - HD 9 (8 cycles) + RT to sites > 2.5 cm
  - HD 12 (4 cycles BE + 4S) + RT
  - HD 15 (6 cycles BE), RT only to PET + sites at end of chemo.
  - All equally effective. HD 15 least toxicity
  - PFS > ~ 75% even in high risk group
- Challenges the role of ABVD as a standard

BEACOPP vs ABVD

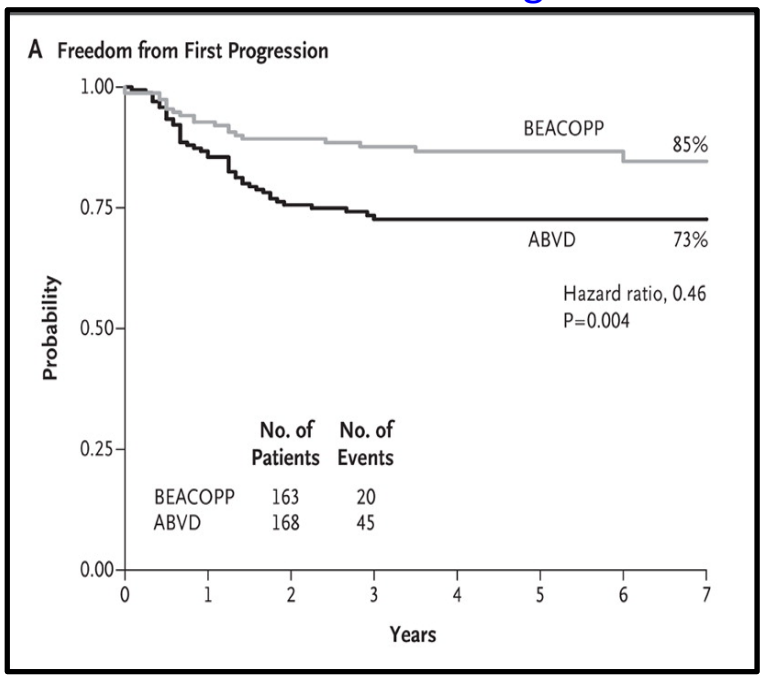
Randomized Trials

- HL 2000 trial (GISL)
  - $BEACOPP_{other}$ $(4B_{esc} + 2B_{bas})$
- Italian cooperative group trial
  - $BEACOPP_{esc} \times 4 + BEACOPP_{bas} \times 4$ (4+4)
- LYSA H34 randomized trial
  - $BEACOPP_{esc} \times 4 + BEACOPP_{bas} \times 4$ (4+4)
- EORTC Intergroup 20012 trial
  - $BEACOPP_{esc} \times 4 + BEACOPP_{bas} \times 4$ (4+4)
- *NONE have used $BEACOPP_{esc} \times 6$ which is the current recommended standard by the GHSG*

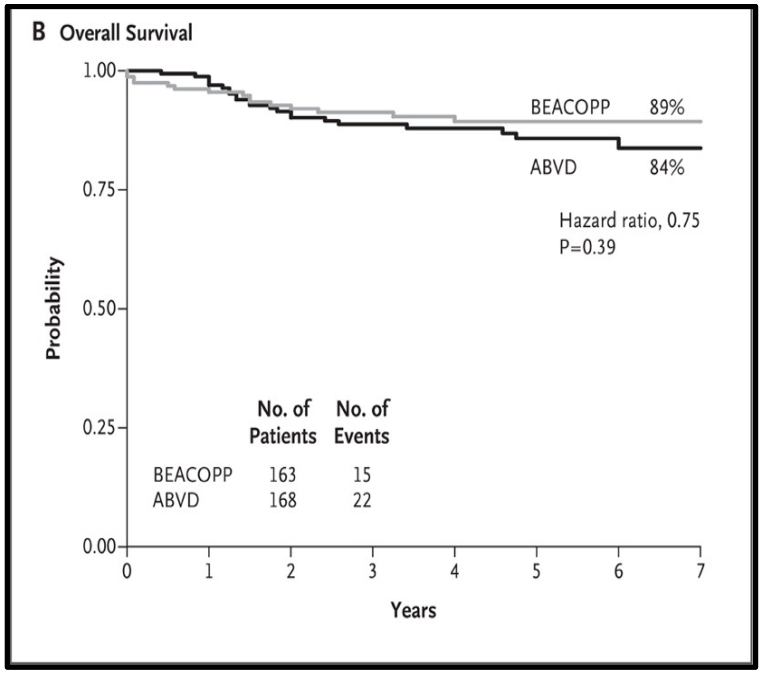
Advanced Hodgkin Lymphoma
Italian Trial: BEACOPP ($4B_{esc}$+ $4B_{std}$) vs ABVD

Michelangelo Foundation; Gruppo Italiano di Terapie Innovative nei Linfomi; Intergruppo Italiano Linfomi

Freedom-from First Progression



Overall Survival

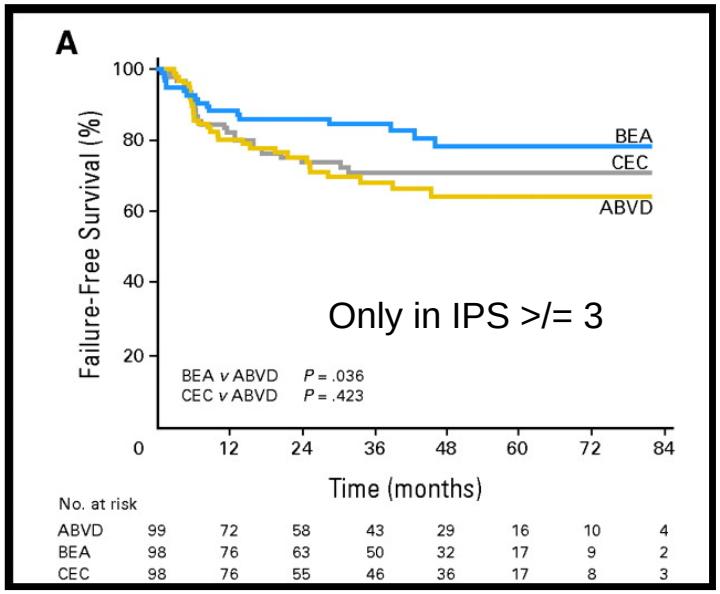


Viviani S et al. NEJM 2011

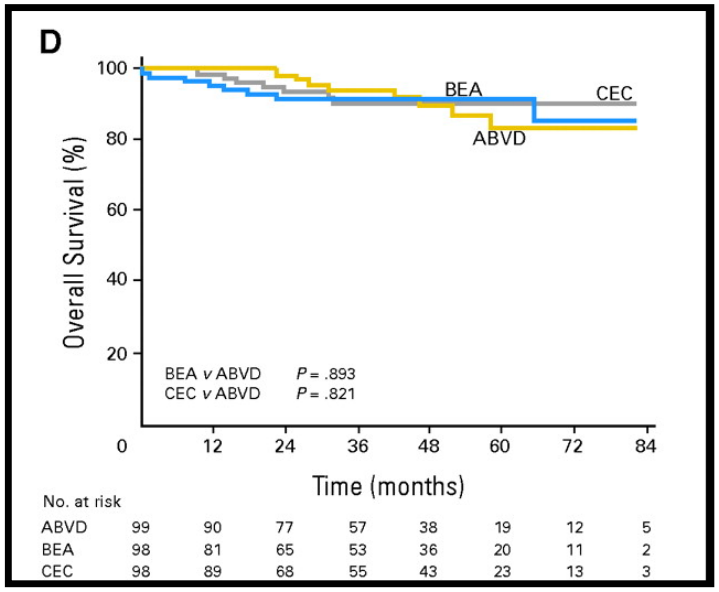
Advanced Hodgkin Lymphoma

Italian HD2000 : BEACOPP (4B $_{esc}$+ 2B$_{bas}$) vs ABVD (IPS >/= 3)

FFS



OS



5-yr PFS: 68%, 81%, 78%
(ABVD, BEACOPP, CEC; P=.038): IPS 0-2 P=.125, IPS 3-7 P=.038
5-yr OS: 84%, 92%, 91%
(ABVD, BEACOPP, CEC; P=NS)

Federico et al. JCO 2009

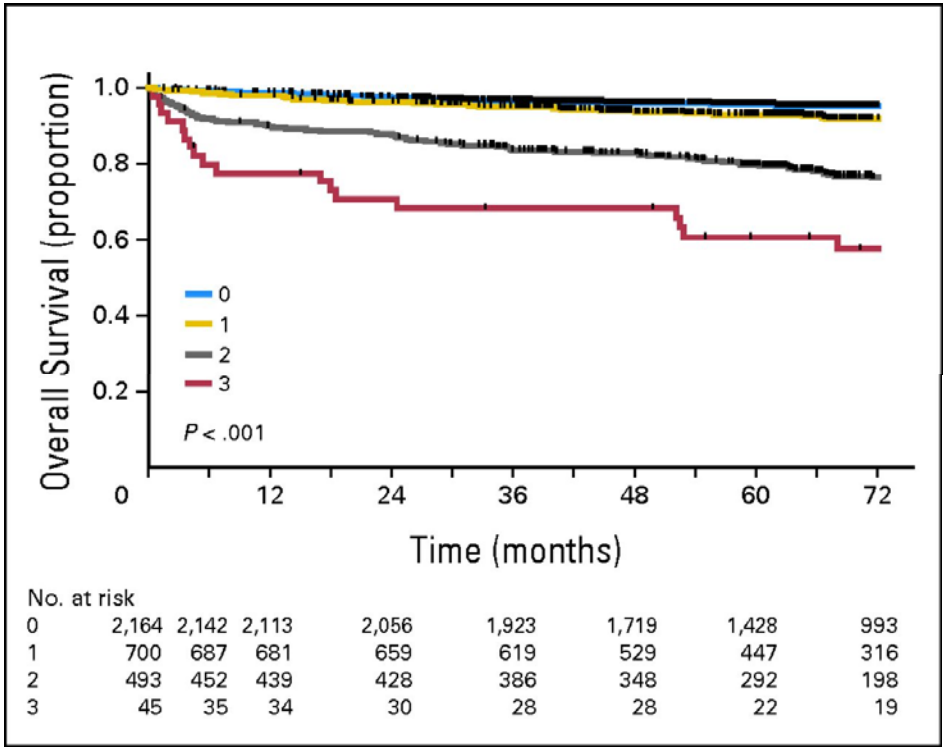
Overall survival according to TRM risk score
esc BEACOPP is not for everybody

3 Point Score

Points: 0 1 2

Age: < 40 41-49 ≥ 50
PS: 0-1 2

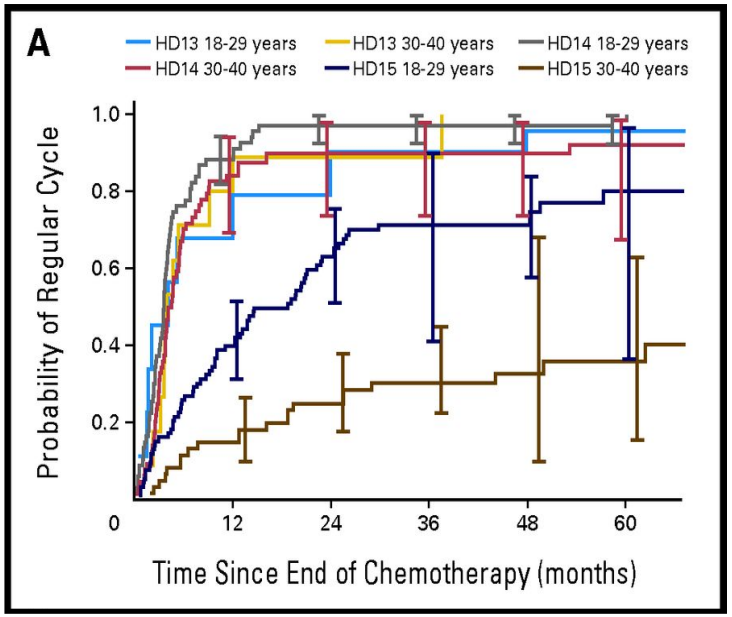
Neutropenic infection commonest cause of death. 70% in cycle 1.

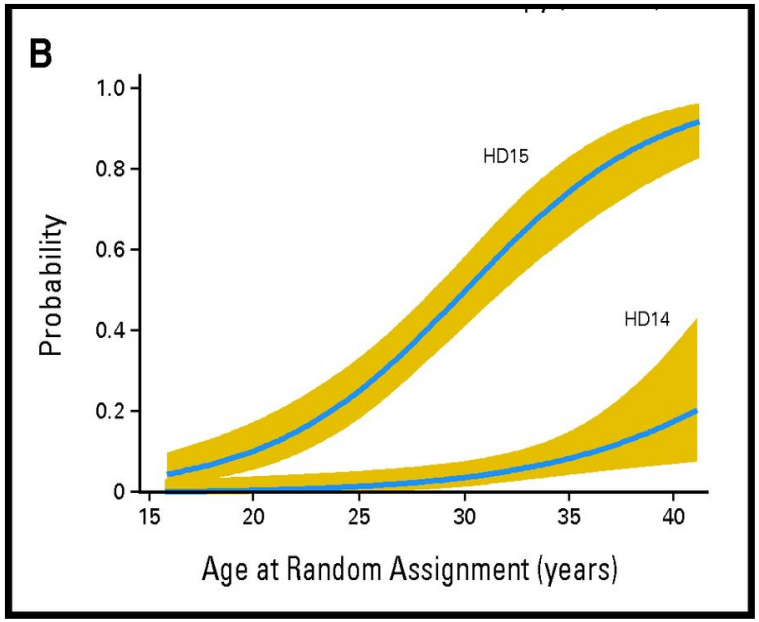


Wongso D et al. JCO 2013

Escalated BEACOPP and Fertility

Probability of resumption of menses is dependent on age and # of cycles of chemotherapy



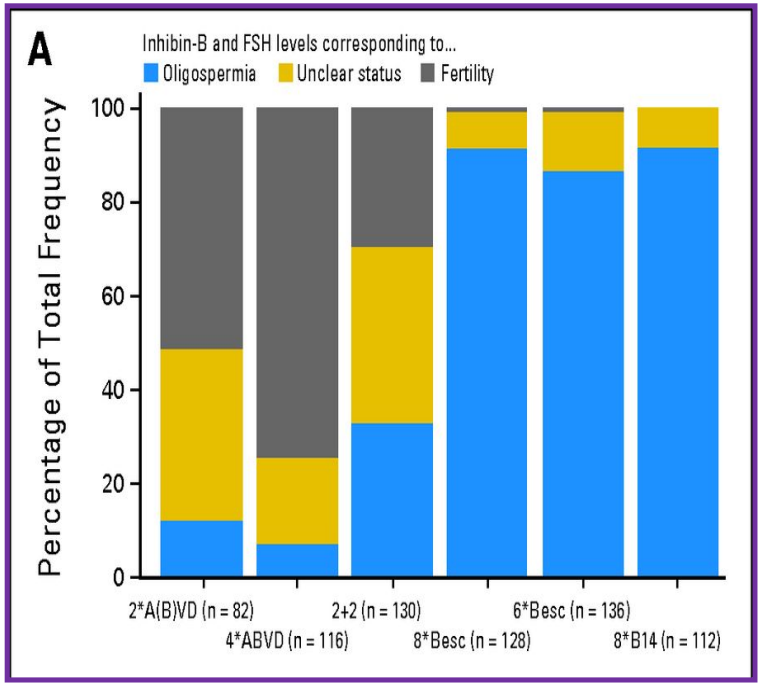


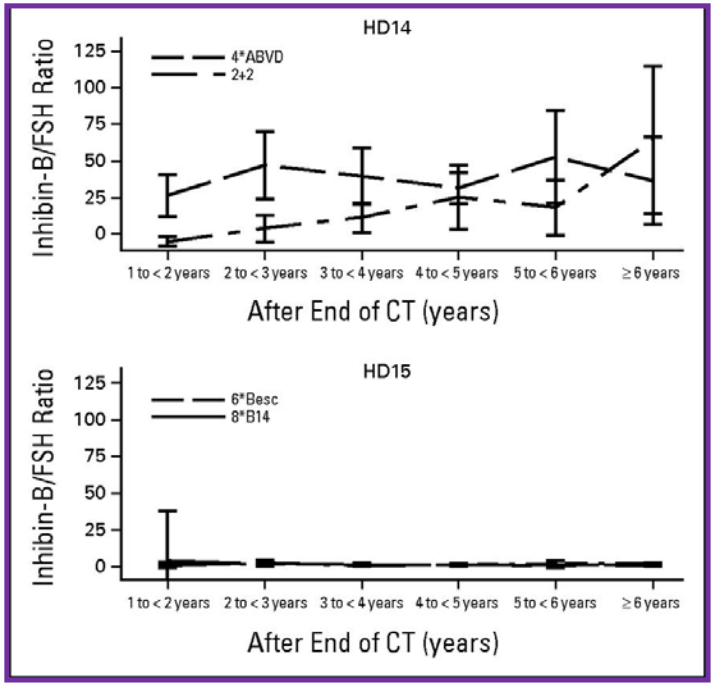
HD 14: 2 ABVD + 2 Esc BEACOPP
HD 15: 6 Esc BEACOPP

Likelihood of amenorrhea at 4 y increases with use of more cycles of Esc BEACOPP

Behringer, et al, JCO 2012

Fertility parameters in men receiving ABVD or Esc BEACOPP





Behringer et al, JCO 2012

Advanced Hodgkin Lymphoma

Summary of BEACOPP data

- PFS is superior with Esc BEACOPP c/w ABVD
  - 4 randomized trials; HR ~0.5
  - PFS benefit across all IPS groups
  - Long term durability is ?? (long term follow up of Italian study)
- OS advantage is challenging to establish.
  - Esc BEACOPP x 8 superior to COPP/ABVD in HD9
  - No OS advantage with BEACOPP in 3 European studies versus ABVD
  - No study has used Esc BEACOPP x 6
- Toxicity issues

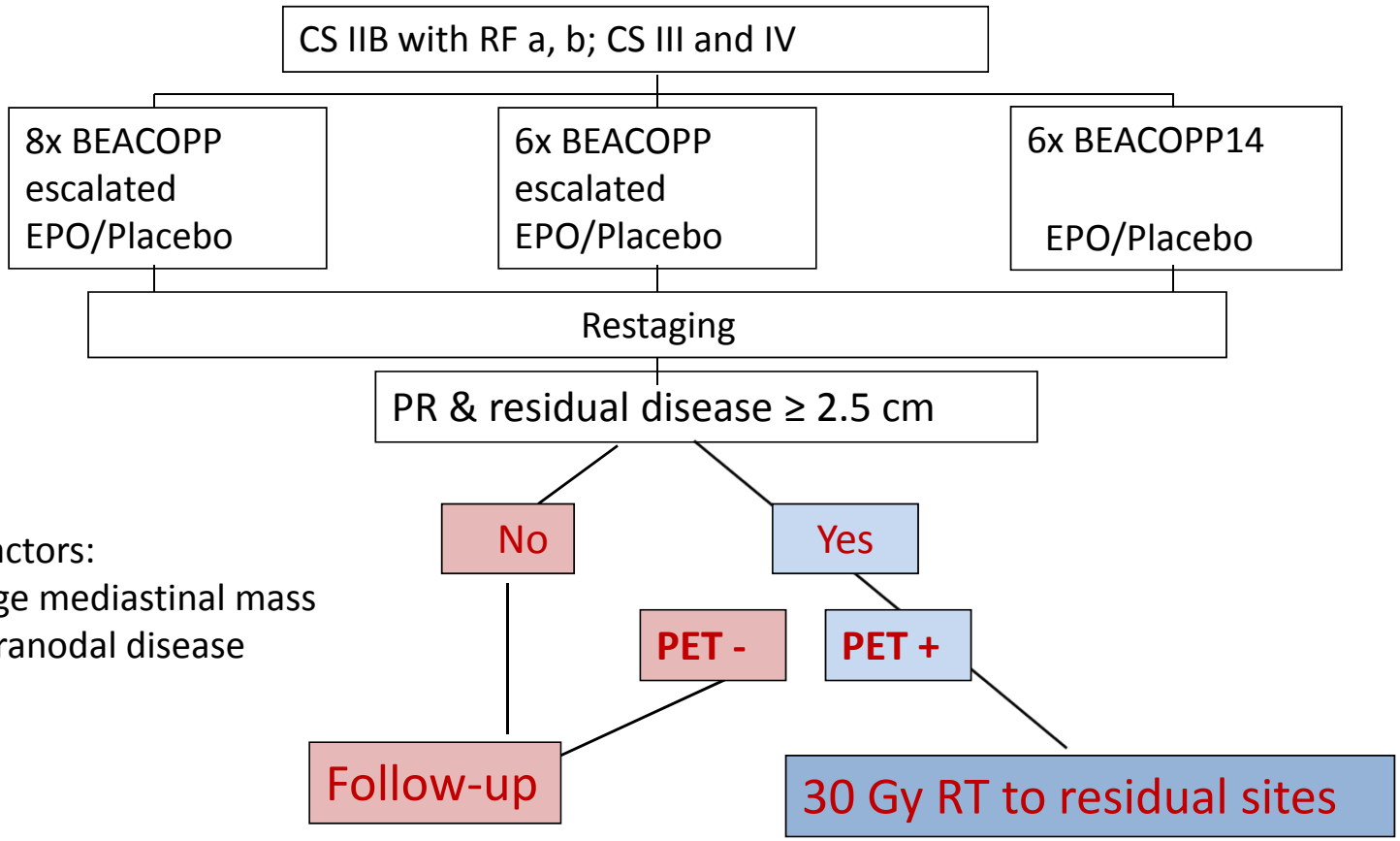
Advanced Hodgkin Lymphoma

Adapting therapy based on PET

HD15	PET+ after Esc BEACOPP x 6 assigned to IFRT
HD18	Esc BEACOPP x 2:
	PET+ randomized to R- Esc BEACOPP vs Esc BEACOPP
	PET- randomized to 4 vs 8 Esc BEACOPP
UK RATHL	ABVD x 2: Escalation to Esc BEACOPP if PET+
	PET- randomized to ABVD vs AVD.
US Intergroup	ABVD x2: Escalation to Esc BEACOPP if PET+

GHSG study for advanced-stage HL (HD15)

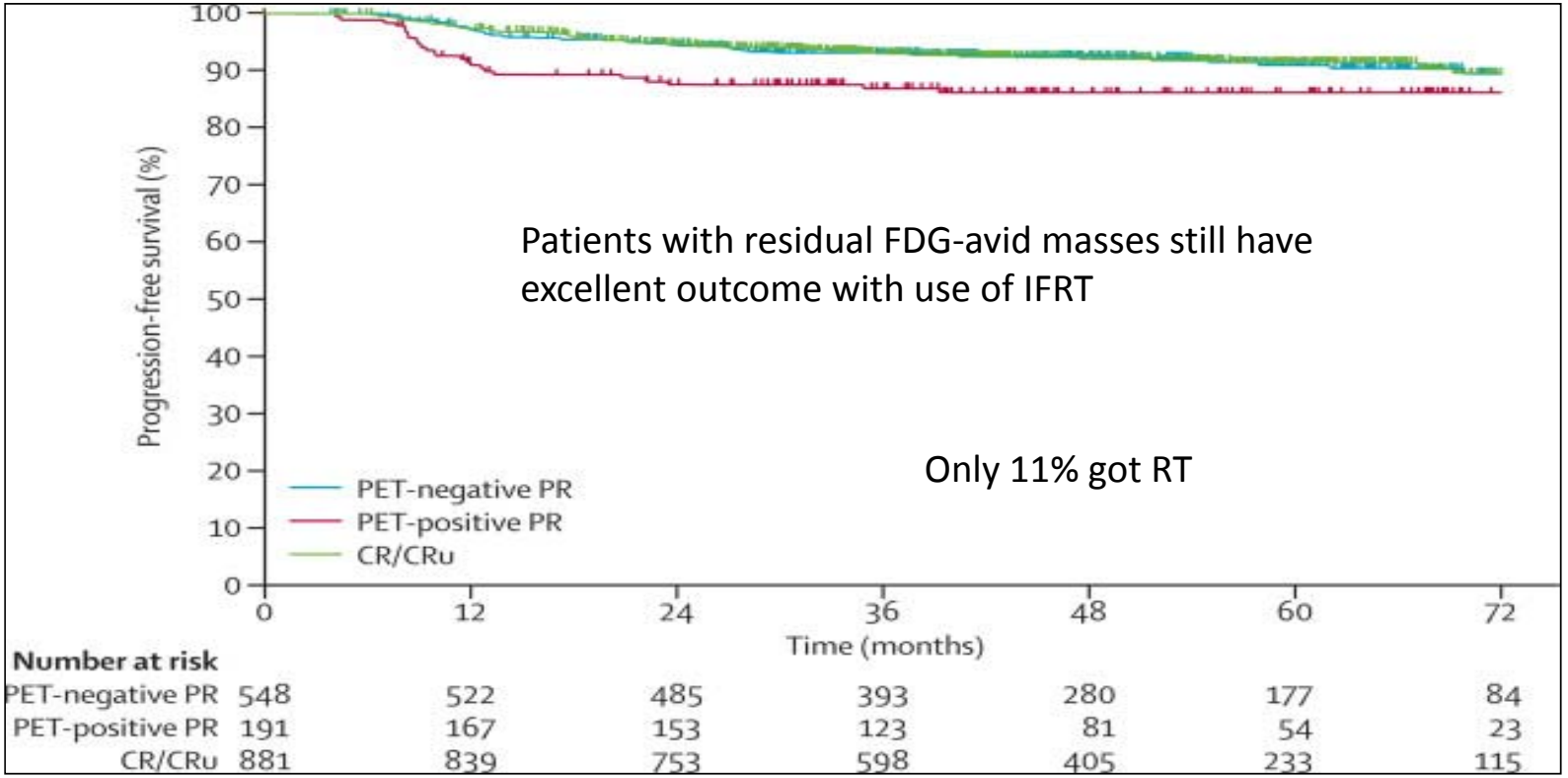
PET assessment of residual tissue in advanced-stage HL



Risk factors:
a) Large mediastinal mass
b) Extranodal disease

Engert et al Lancet 2012

PET-guided radiotherapy in advanced stage HL (HD15 trial):



Patients with residual FDG-avid masses still have excellent outcome with use of IFRT

Only 11% got RT

Engert et al Lancet, 2012

Addition of Rituximab to BEACOPP$_{escalated}$ to Improve the Outcome of Early Interim PET Positive Advanced Stage HL: Second Planned Interim Analysis of the HD18 Study. (ASH 2014 Borchmann et al, abstract 500)

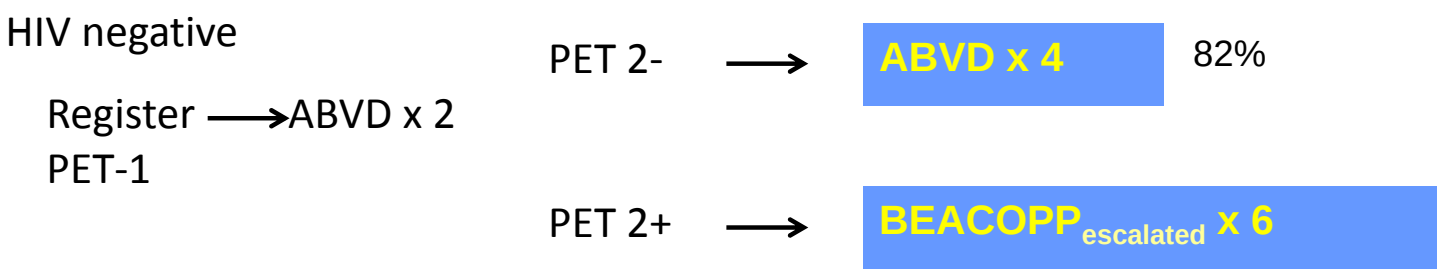
- PET-2 positive patients have a poorer outcome
- Targeting the microenvironment in HL with the anti-CD20 antibody rituximab had been shown to be active in clinical studies both as single agent and in combination with ABVD
  - Younes et al. BLOOD 2012
- QS: Rituximab as a combination partner for BEACOPP in early interim PET positive patients (Improve 5 y PFS from 68% to 83%)?
- Treatment reduction for early interim PET negative patients ie reduce number of cycles of esc BEACOPP.

Conclusions

- After a negative interim FDG-PET scan it is safe to omit bleomycin from subsequent cycles, without consolidation radiotherapy
- Omission of bleomycin reduces toxicity, especially dyspnoea, thromboembolism and neutropenic fever
- Escalated therapy for interim FDG-PET positive patients gives good subsequent response rates, and promising PFS results (70% 3 year PFS for PET-3 negatives)
- The 'false-negative' rate for interim FDG-PET is higher among patients with more advanced stage disease
- Overall results from this study appear better than our previous trials, using more selective chemotherapy and less radiotherapy

A Phase II US Intergroup Trial of Response-Adapted Therapy of Stage III-IV HL Using Early Interim FDG-PET Imaging (SWOG S0816)

Preliminary Results



IPS 0-7, No RT either arm

Goals:

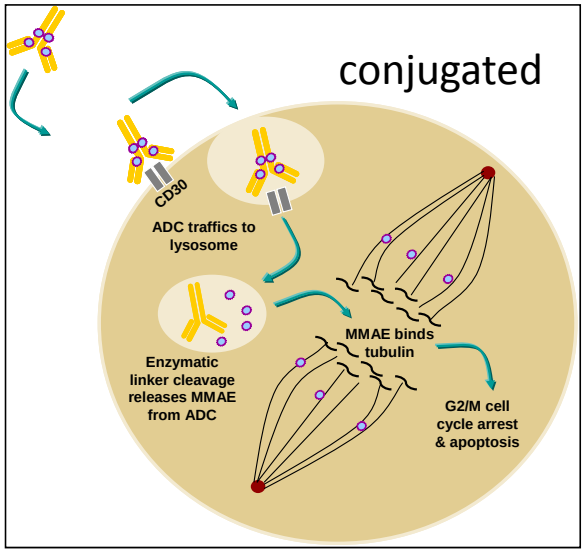
- Increase 2-yr PFS from historical value of 70% with ABVD to 78% with PET response adapted therapy.
- Increase 2-yr PFS of PET2+ from 15-30% if continued on ABVD to 48% with PET response adapted therapy.

Courtesy Dr Johnson ICML 2015

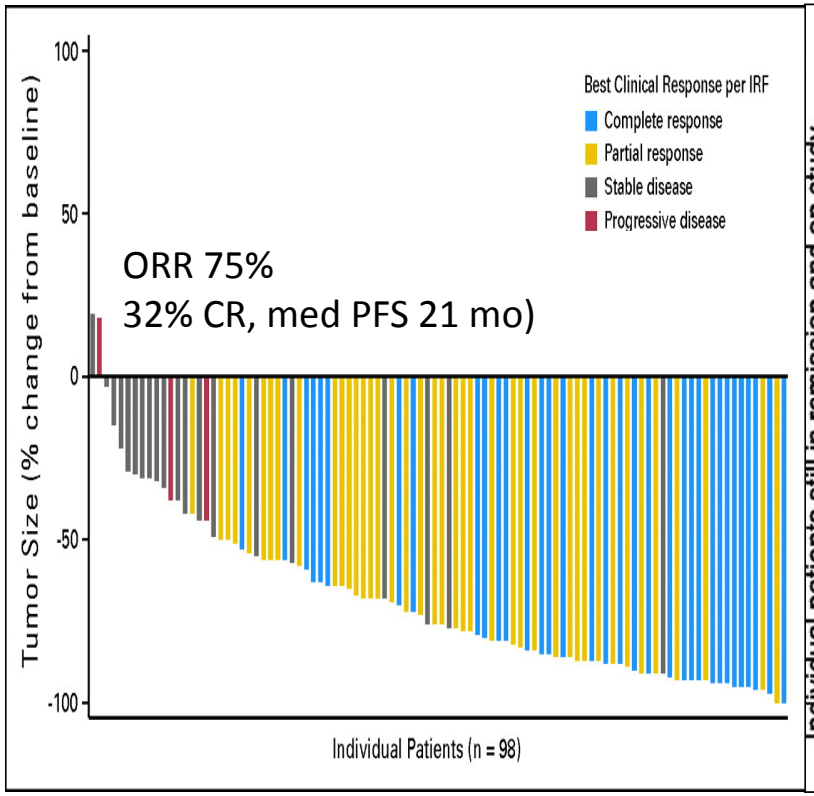
Incorporation of new agents in front line therapy

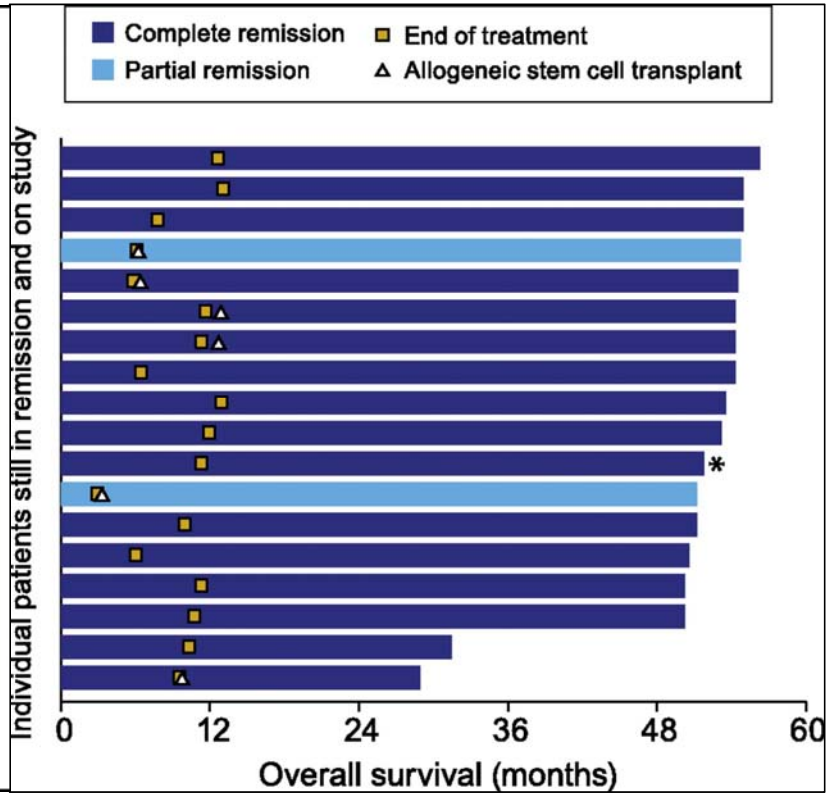
Brentuximab Vedotin (SGN-35)

- CD30 Antigen
  - Transmembrane glycoprotein receptor, TNF receptor superfamily
  - Cell surface Ag highly expressed in Hodgkin & ALC Lymphoma
  - Normal distribution restricted to activated T and B cells, macrophages
- SGN-35 antibody-drug conjugate
  - CD30-targeted antibody (cAC10) to an auristatin (MMAE), an anti-tubulin agent
- Selective apoptosis in HL and ALCL
  - Binds to CD30
  - Becomes internalized
  - Releases MMAE
- Phase I q 3 wk SGN-35 trial
  - MTD 1.8 mg/m2, ORR 54% (CR 32%)
  - DLTs neutropenia, hyperglycemia, unrelated ARF



Phase II Pivotal trial in relapsed HL
All ASCT failures

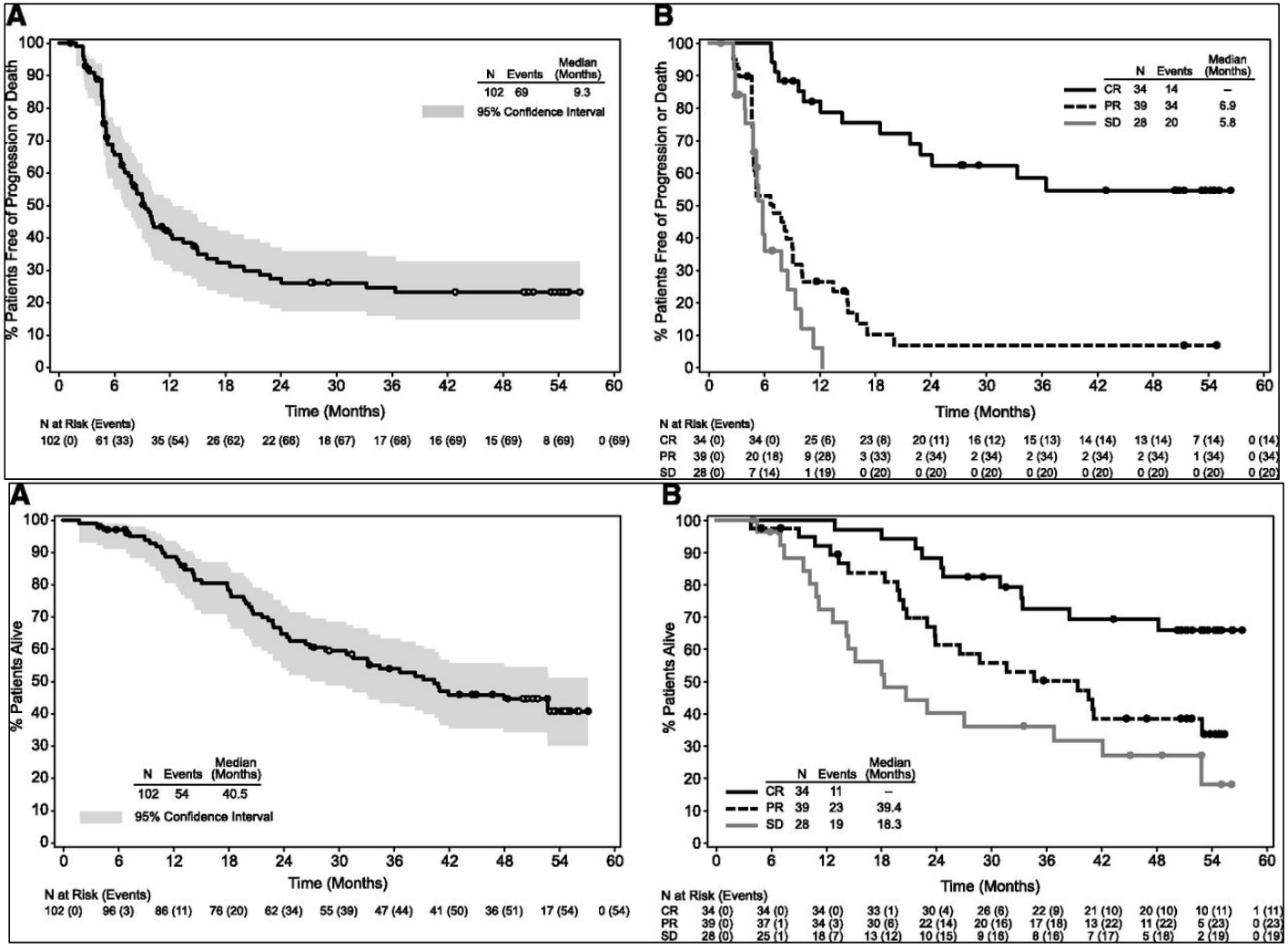




Younes et al JCO 2012

A Gopal et al. Blood 2015

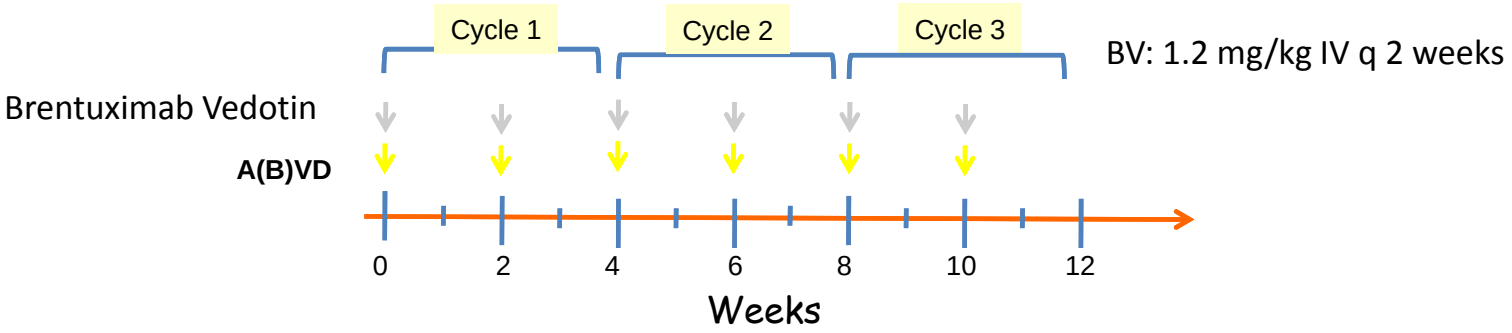
PFS and OS following treatment with Brentuximab Vedotin



Ajay K. Gopal et al. Blood 2015;125:1236-1243

Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Pts with Newly Diagnosed Advanced Stage HL

- Major Eligibility
  - Treatment-naive HL patients
  - Age ≥18 to ≤60 years
  - Stage IIAX or Stage IIb-IV disease
- Treatment Design
  - 28-day cycles (6 cycles) with dosing on Days 1 and 15



Younes et al. Lancet Oncology 2013

Toxicity and Efficacy

	Brentuximab vedotin and ABVD group (n=25)	Brentuximab vedotin and AVD group (n=26)
Any event	11 (44%)	0
Pulmonary toxic effects	9 (36%)	0
Interstitial lung disease	1 (4%)	0
Pneumonitis	1 (4%)	0

Events generally occurred during Cycles 3–4

Two deaths were associated with pulmonary toxicity

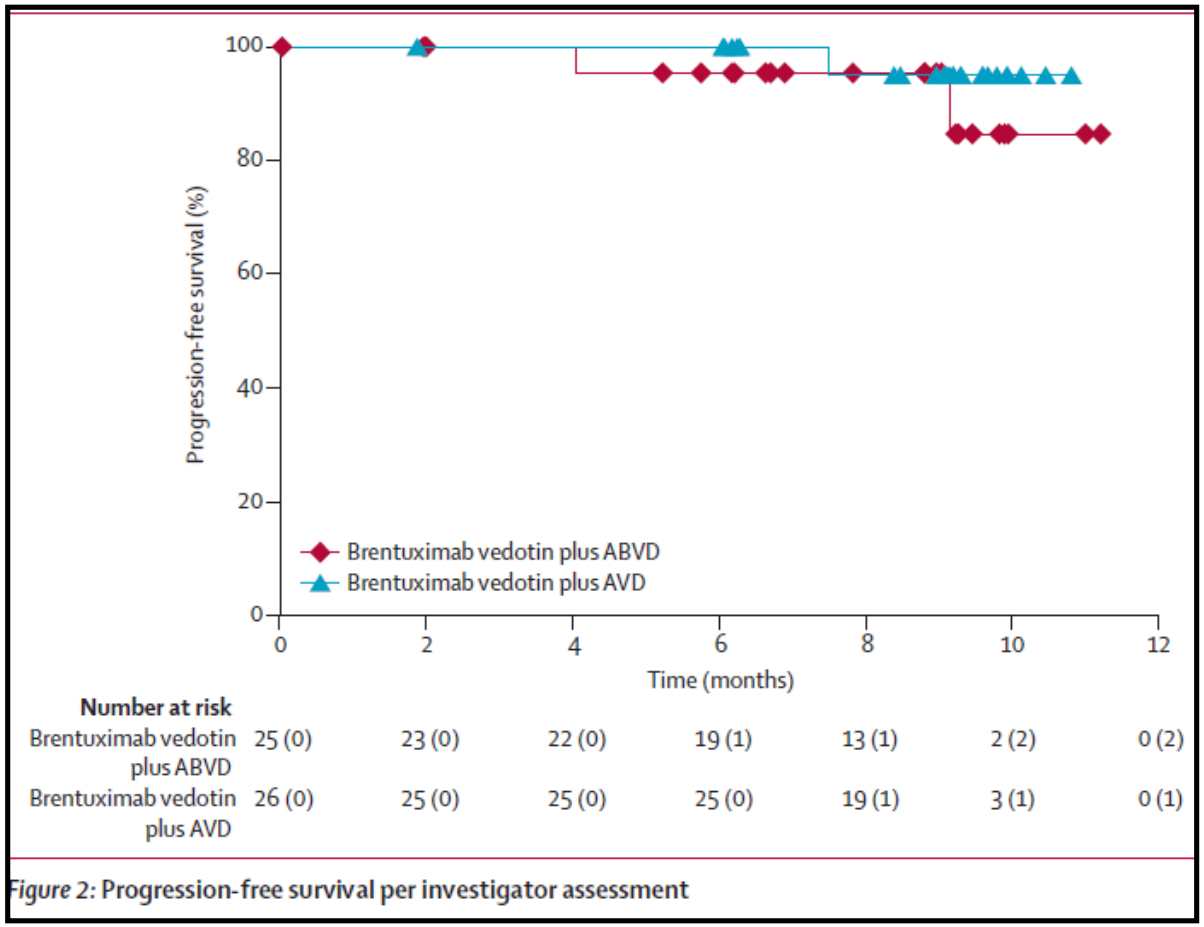
Events resolved in 9 of 11 patients (82%)

Median time to resolution 2.6 weeks (range, 1.6 to 5 weeks)

	Brentuximab vedotin and ABVD group (n=25)	Brentuximab vedotin and AVD group (n=26)
Cycle 2 PET scan per IRF*	22†	26
Negative	22 (100%)	24 (92%)
Positive	0	2 (8%)
Best response at end of front-line treatment per investigator	22‡	25§
Complete response	21 (95%)	24 (96%)
Progressive disease	0	1 (4%)
Not evaluable¶	1 (5%)	0
95% CI for complete response‖	77·2–99·9	79·7–99·9

Younes et al. Lancet Oncology 2013

Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Pts with Newly Diagnosed Advanced Stage HL



Number at risk							
Brentuximab vedotin plus ABVD	25 (0)	23 (0)	22 (0)	19 (1)	13 (1)	2 (2)	0 (2)
Brentuximab vedotin plus AVD	26 (0)	25 (0)	25 (0)	25 (0)	19 (1)	3 (1)	0 (1)

Figure 2: **Progression-free survival per investigator assessment**

Younes et al. Lancet Oncology 2013

Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Pts with Newly Diagnosed Advanced Stage HL

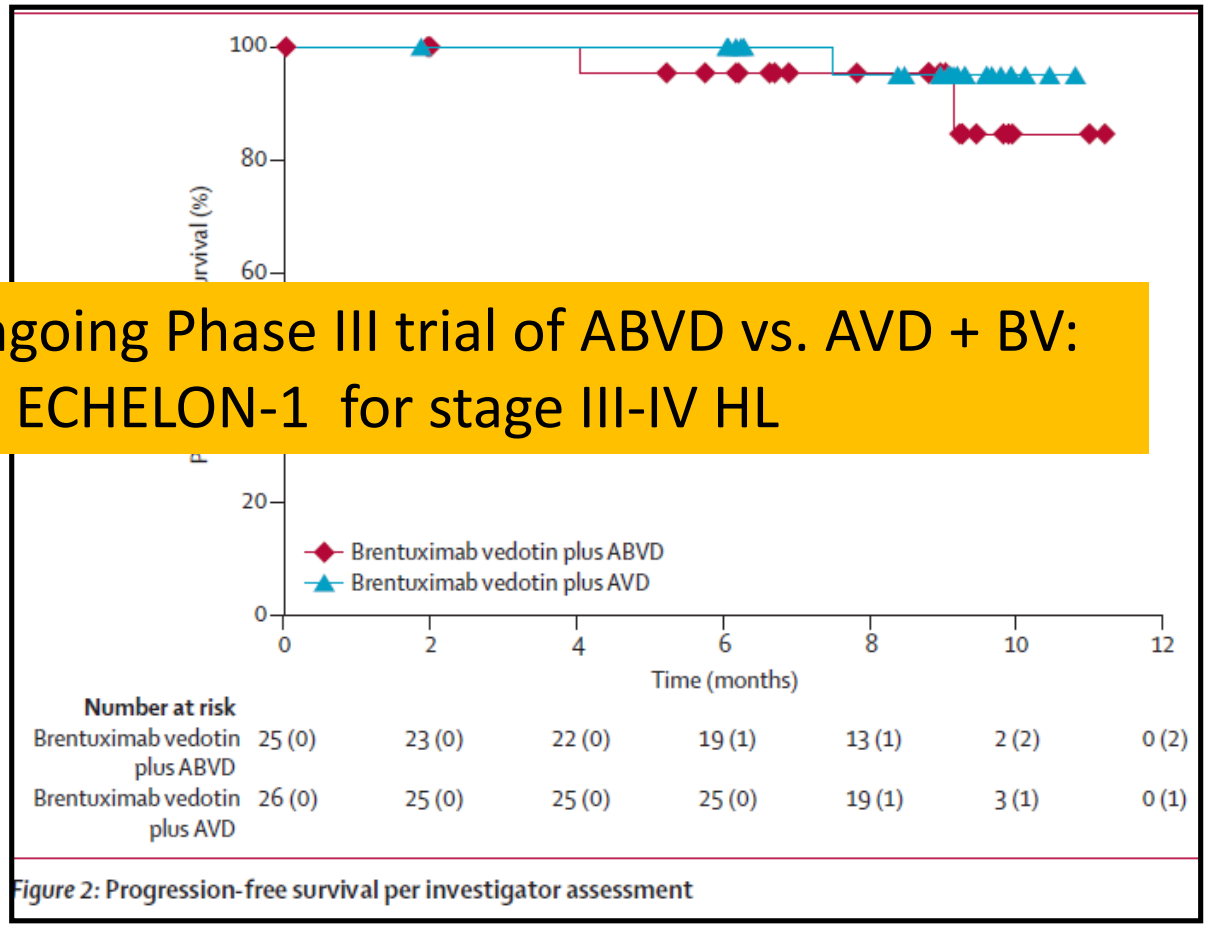


Figure 2: **Progression-free survival per investigator assessment**

Ongoing Phase III trial of ABVD vs. AVD + BV: ECHELON-1 for stage III-IV HL

Younes et al. Lancet Oncology 2013

Advanced Hodgkin Lymphoma
Take Home Message

- Newer criteria for PET/CT interpretation need to be used for risk adapted strategies
  - Dialog with nuclear medicine colleagues important
- The frontline treatment for advanced stage Hodgkin lymphoma remains ABVD
  - Brentuximab containing combinations under study, with AVD only
  - Escalation to esc BEACOPP if PET + after ABVD x 2 promising
  - Bleomycin can be omitted if PET negative after 2 cycles of ABVD
- No prospective data on other strategies (eg IFRT to +ve areas after ABVD x 6-8 as in GHSG HD15)

Management of Hodgkin Lymphoma

What is the optimal therapy for individual patients?

Highest cure rate with primary therapy

Fewest complications for optimal survivorship

NCCN Member Institutions